Clinical Update

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Bisphosphonate-associated osteonecrosis of the jaws

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Introduction

"Oral complications resulting from drug therapy and medical procedures have been an important, challenging subject for clinicians and researchers interested in oral disease for decades."(1) Chemical or pharmacologic agent involvement in the development of necrosis of the jaws is not a new phenomenon. The use of yellow phosphorus in matchmaking in the 19th century led to a condition known as "phossy jaw" (2,3,4). Today, clinicians are faced with another entity causing necrosis of the jaws with a similar appearance to that of "phossy jaw." Many cancer patients with osteolytic processes (e.g. multiple myeloma, prostate cancer, breast cancer) are being treated with bisphosphonate medications for the skeletal complications and hypercalcemia of malignancy (5). These medications are also being used in the prevention of osteoporosis.

Bisphosphonate pharmacology

The bisphosphonate class of medication includes drugs such as pamidronate (Aredia®, Novartis, East Hanover, NJ), zolendronate (Zometa®, Novartis, East Hanover, NJ), and alendronate (Fosamax®, Merck, Whitehouse Station, NJ). These drugs are compounds that contain a Phosphate-Carbon-Phosphate structure and are nitrogen-containing compounds. They bind to the surface of bone through absorption to the exposed mineral, calcium hydroxyapatite. This binding preferentially occurs at sites undergoing active resorption. At a molecular level, nitrogen-containing bisphosphonates inhibit sterol biosynthesis via inhibition of farnesyl diphosphate synthase (FFP). At the cellular and tissue levels, this inhibition of FFP within osteoclasts causes a loss of attachment to the bone surface and osteoclast inactivation resulting in decreased bone resorption and increased bone mineralization (6). Non-nitrogen-containing bisphosphonates (etidronate, clodronate, tiludronate) induce osteoclast apoptosis through incorporation into ATP analogues (7). Bisphosphonates have also been shown to be anti-angiogenic (8,9) secondary to inhibition of vascular endothelial growth factor (8).

Patient presentation

There are several case series identifying a growing problem with oral complications associated with the use of bisphosphonate therapy (particularly with zolendronate and pamidronate) for skeletal complications and hypercalcemia of malignancy (9-14). Although this does not prove causality, the identification of commonality and development of a plausible hypothesis deserves increased caution on the part of clinician and further research (15).

Patients characteristically present with a complaint of pain accompanied by soft tissue ulceration and/or more commonly exposed bone. Patients typically have difficulty eating, swallowing or speaking secondary to pain. The exposed bone may progress to frank sequestration. Biopsy results of such lesions show only non-vital bone and localized inflammatory response consistent with the clinical presentation. Patients present with lesions in both the maxilla and the mandible. Typically, the lesions are seen during a variable period following surgical procedures in the oral cavity, including: extractions, periodontal surgery, and surgical endodontics, although some lesions have been noted to occur spontaneously.

In Marx's series of 36 cases, 78% occurred after dental extractions and 22% were spontaneous (12). Migliorati reported five cases, 2 following extractions and 3 spontaneous (9). Estilo et al., in their series of 13 cases, reported 9 cases following extraction and 4 occurring spontaneously (11). At the National Naval Medical Center (NNMC), there currently are a case series of three (two affecting the mandible and 1 affecting the maxilla) all occurring after intraoral surgical procedures (extraction, periodontal treatment, and surgical endodontics). Biopsy results from the NNMC patients have specifically commented that there was no evidence of osteomyelitis, and therefore, no evidence of an associated infectious process.

Treatment

Consistent successful treatment of these lesions has thus far been elusive (9,10,12,13). Surgical treatments that have been attempted are local debridement, sequestrectomy and marginal or segmental resections. However, further surgical intervention does not seem to halt the progression of the lesion and in some cases exacerbates the lesion. Antibiotics (particularly penicillin and metronidazole for 6 – 12 months if no allergy exists) have been unpredictably successful and are dependent on patient compliance. Tetracycline and erythromycin have also been used with equivocal success in penicillin allergic patients (12). Hyperbaric oxygen therapy has not been effective. The most common treatments at this time are controlling the patient's pain and observation through routine follow-ups for management of any localized infectious process with local debridement and Peridex® (Zila Pharmaceuticals, Phoenix, AZ).

Summary

New applications for bisphosphonates are continually being investigated: 1) reduction in periodontal bone loss; 2) treatment of fibrous dysplasia; 3) treatment of avascular necrosis of the hip; 4) treatment of complex regional pain syndrome; and 5) treatment of other malignancies (e.g. melanoma) (8,16-20).

As expanded uses for these medications are found, the potential for complications from their use also increases. Vigilance on the part of dentists in regards to the patient's past medical history and current medication regimen is paramount to reduce the morbidity to the patient. In an effort to increase awareness of potential complications, Novartis recently added a warning label to their products and sent a letter to all healthcare providers recommending a dental examination with appropriate preventive dentistry treatment prior to beginning bisphosphonate therapy (21). Goss has recommended the following protocol in consultation with the patient's oncologist: 1) discontinuance of bisphosphonate therapy for at least 2 months prior to any surgery and 2) restarting of bisphosphonate therapy no sooner than 2 months postoperatively (10).

Recommendations

We recommend comprehensive dental screenings similar to those for pre-radiation treatment for head and neck cancer patients. We also recommend that patients undergoing any required invasive dental procedures allow a minimum 2-month healing period prior to initiating bisphosphonate therapy. We base these recommendations on the protocol used for pre-radiation treatment of head and neck cancers and Dr. Goss' protocol. Close coordination with the patient's oncologist is mandatory. It is also recommended that patients be properly counseled about this potential complication prior to initiating bisphosphonate therapy and prior to undergoing any invasive dental procedure following initiation of bisphosphonate therapy (1).

References:

1. Greenberg MS. Intravenous bisphosphonates and osteonecrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004 Sep;98(3):259-60.
2. Miles AE. Phosphorus necrosis of the jaw: 'phossy jaw'. Br Dent J. 1972 Sep;133(5):203-6.
3. Hellstein JW, Marek CL. Bis-phossy jaw, phossy jaw, and the 21st century: bisphosphonate-associated complications of the jaws. J Oral Maxillofac Surg. 2004 Dec;62(12):1563-5.
4. Jakhi SA, Parekh BK, Gupta S. Phosphorus necrosis of the maxilla. J Oral Med. 1983;38(4):174-6.
5. Body JJ, Diel I, Bell R. Profiling the safety and tolerability of bisphosphonates. Semin Oncol. 2004 Oct;31(5 Suppl 10):73-8.
6. Reszka AA, Rodan GA. Nitrogen-containing bisphosphonate mechanism of action. Mini Rev Med Chem. 2004 Sep;4(7):711-9.
7. Rodan G, Reszka A, Golub E, Rizzoli R. Bone safety of long-term bisphosphonate treatment. Curr Med Res Opin. 2004 Aug;20(8):1291-1300.
8. Yamagishi S, Abe R, Inagaki Y, Nakamura K, Sugawara H, Inokuma D, et al. Minodronate, a newly developed nitrogen-containing bisphosphonate, suppresses melanoma growth and improves survival in nude mice by blocking vascular endothelial growth factor signaling. Am J Pathol. 2004 Dec;165(6):1865-74.
9. Migliorati CA. Bisphosphonates and oral cavity avascular necrosis. J Clin Oncol. 2003 Nov 15;21(22):4253-4.
10. Carter GD, Goss AN. Bisphosphonate and avascular necrosis of the jaws. Aust Dent J. 2003 Dec;48(4):268.
11. Estilo CL, Van Poznack CH, Williams T, Evtimovska E, Tkach L, Halpern JL, et al. Osteonecrosis of the maxilla and mandible in patients treated with bisphosphonates: a retrospective study. J Clin Oncol. 2004 Jul;22(14 Supplement):750S.
12. Marx RE. Pamidronate (Aredia) and zolendronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003 Sep;61(9):1115-7.
13. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg. 2004 May;62(5):527-34.
14. Pogrel MA. Bisphosphonates and bone necrosis. J Oral Maxillofac Surg. 2004 Mar;62(3):391-2.
15. Tarassoff P, Csermak K. Avascular necrosis of the jaws: risk factors in metastatic cancer patients. J Oral Maxillofac Surg. 2003 Oct;61(10):1238-9.
16. Altundal H, Guvener O. The effect of alendronate on resorption of the alveolar bone following tooth extraction. Int J Oral Maxillofac Surg. 2004 Apr;33(3):286-93.
17. Tenenbaum HC, Shelemay A, Girard B, Zohar R, Fritz PC. Bisphosphonates and periodontics: potential applications for regulation of bone mass in the periodontium and other therapeutic/diagnostic uses. J Peridontol. 2002 Jul;73(7):813-22.
18. Kos M, Luczak K, Godzinski J, Klempous J. Treatment of monostotic fibrous dysplasia with pamidronate. J Craniomaxillofac Surg. 2004 Feb;32(1):10-5.
19. Agarwala S, Sule A, Pai BU, Joshi VR. Alendronate in the treatment of avascular necrosis of the hip. Rheumatology. 2002 Mar;41(3):346-7.
20. Robinson JN, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome Type 1. Pain Med. 2004 Sep;5(3):276-80.
21. MedWatch 2004. Available from: URL http://www.fda.gov/medwatch/SAFETY/2004/safety04.htm#zometa. Accessed October 20, 2004.

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